b.) Remarks

Claim 26-51 are presented in order to recite Applicants' invention with the specificity required by statute. The subject matter of the claims is found in the application as filed, *inter alia*, both in the original claims and in the specification at e.g., page 8, lines 12-17, page 9, lines 16-19, from page 11, line 23 to page 12, line 11, page 15, lines 13-16 and from page 12, line 20 to page 13, line 22. Accordingly, no new matter has been added.

The Examiner has objected to the Information Disclosure Statement for the reasons noted.[1/] In this regard, it is unclear why 37 C.F.R. §1.98(b) (5) was cited for disallowing the citation format; MPEP §707.05(e) makes plain that

> [f]or periodicals, at least the title of the periodical, the volume number, date, and pages should be given.

Applicants' PTO-1449 was plainly in compliance therewith. Nonetheless, to reduce the issues, enclosed is a substitute form PTO-1449. As requested by the Examiner, authors and titles are provided

To the extent the Examiner's notations "No translation" appear, Applicants' respectfully wish to point out that no translation is necessary if a concise explanation of the reference's relevance as presently understood is provided ("which may be incorporated in Applicants' specification"), see 37 C.F.R. §1.98(a)(3)(i). As noted in the July 19, 2001 Information Disclosure Statement, such is found both in the specification where the Examiner's attention was invited, as well as in the respective English-language abstracts.

The Examiner also requested a complete copy of page 276 from J. Clin. Exp. Med., Vol 172, No. 5 (1995). In response, such replacement sheet is enclosed.

1/ As to the Examiner crossing out the citations on the form PTO-1449, it is assumed the references were considered since the form only indicates how the art will apear on the face of an issued patent. Clarification is respectfully requested.

Claims 1-18 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner's bases for this rejection are set forth at pages 3 and 4 of the Office Action. These comments have been addressed in new claims 26-51. The Examiner's detailed suggestions are gratefully acknowledged.

Claim 1 is rejected under 35 U.S.C. §102(b) as anticipated by JP 57-137858; claims 1 and 2 by JP 59-011197 or Yoshida, Nissei Byoinlgalev Zasshi 12(1):53-7 (1984) and claims 1-5, 7-13 and 15-18 by JP 58-047499. Additionally, claims 1-3, 15, 16 and 18 are rejected under 35 U.S.C. §103(a) as obvious over Yoshida in view of Sanders, U.S. Patent No. 4,215,993 or EP 76211, and claims 1-12, 14, 15, 17 and 18 over Ohkubo et al., Rinsho Kensa 27(3):329-32 (1983) in view of Sanders or EP 76211.

These rejections are respectfully traversed and will be addressed below in turn.

For the Examiner's convenience, it should be noted that claims 26 and 39 only are independent. Claim 26 corresponds to original claim 3, claim 39 to original claims 8 and 9. Accordingly, the rejections for anticipation by JP 57-137858, JP 59-011197 and Yoshida are mooted.

As to JP 58-047499 (which the Examiner relies upon as quantitating triglycerides by treating serum with surfactant such as Triton X 100 and the like) claim 26 recites, in part, reacting a sample containing a mixture of lipoproteins in the presence of a reagent which inhibits reaction of lipoproteins other than the particular lipoprotein, enzymatically reacting that sample to generate hydrogen peroxide, and quantitating generated hydrogen peroxide. Claim 39 similarly recites determination from a sample containing a mixture of lipoproteins, in part, in the presence of a reagent that allows reaction of lipoprotein other than the particular one, reacting that sample without free glycerol in the presence of a surfactant or enzyme that allows the reaction of the particular

lipoprotein, enzymatically reacting the sample to generate hydrogen peroxide, and quantitating generated hydrogen peroxide. These features, at least, are not taught or suggested by JP 58-047499.

As to the rejection for obviousness over Yoshida in view of Sanders and EP 76211, Yoshida is cited only as determining triglyceride by eliminating free glycerol to generate peroxide and to subsequently generate color from the peroxide. However, the reference is unconcerned, at least, with assaying a sample containing a mixture of lipoproteins and this deficiency is not overcome by the secondary references to Sanders or EP 76211. Both Sanders and EP 76211 describe quantitating a material by fractionating a particular lipoprotein from a sample by centrifugation; isolating a sample containing the fractionated lipoprotein; and reaction with a particular enzyme.[2/] However, neither teach or suggest concerning a quantitation without isolating the target material, much less a method of quantitating a particular lipoprotein in a sample containing as well as a lipoprotein other than the particular lipoprotein.

As to the rejection of claims 1-12, 14, 15, 17 and 18, the Examiner states Ohkubo teaches quantitating transglyceride using glycerol oxidase, Sanders shows separating lipoprotein using polyanions and EP 76211 teaches separating lipoprotein using surfactants and polyanion/divalent metals. The Examiner contends it would have been obvious to combine Sanders or EP 76211 with the process of Ohkubo to quantitate a particular lipoprotein.

However, as discussed previously, none of these relate to enzymatically quantitating a particular lipoprotein in a sample containing a lipoprotein other than the

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2/ See Sanders, column 2 at lines 29 to 45 where a precipitating reagent is reacted to separate the sample to a precipitate and a supernatant fluid, to separate the supernatant fluid from the precipitate, and an enzyme is reacted only to the supernatant fluid to quantitate the desired material. Also, see the abstract EP 76211 at line 5, where it is described that the separation is executed by centrifugation.

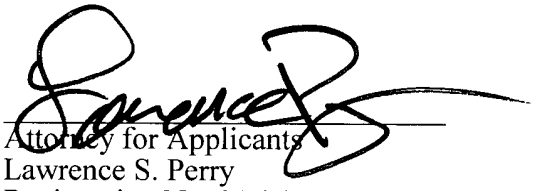
particular lipoprotein.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 26-51 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



Attorney for Applicants
Lawrence S. Perry
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

NY_MAIN 378327v1

FORM PTO 1449 (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(Use several sheets if necessary)

ATTY DOCKET NO.	APPLICATION NO.
02603.000002	09/889,742

APPLICANT	
Kazuhito Miyauchi, et al.	
FILING DATE	GROUP
July 20, 2001	1651

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES/NO/ OR ABSTRACT

OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

		Taku Yamamura, et al., Apoliprotein E and Atherosclerosis, Arteriosclerosis, Vol. 25, Nos. 11, 12 (1998), pages 415-419
		Taku Yamamura, et al., Familial Type III Hyperlipoproteinemia, Journal of Clinical and Experimental Medicine, Vol. 172, No. 5 (1995), pages 276-280,
		Yoshiyatlata, Triglycerides and Atherosclerosis, Journal of Clinical and Experimental Medicine, Vol. 164, No. 12 (1993), pages 833-836
		Tamie Ando, Monoclonal Antibody: Introduction of Experimental Procedure, Kodansha Scientific (1991), page 21
		Toshio Kajiuchi et al., Stability and Partition of Modified Cellulase in Water-Benzyme, Toluene System, Journal of Chemical Engineering of Japan, Vol. 20, No. 3 (1994), pages 459-462

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

家族性

家族性III型高脂血症

山村　卓

◉III型高脂血症は，通常の血中にはほとんど存在しないβ-VLDLとよばれる異常なリポ蛋白がうっ滞する．アポEの遺伝性異常に基づくレムナントの代謝障害によって発症する．

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キーワード：アポE，高脂血症，動脈硬化，リポ蛋白，レムナント・リポ蛋白

III型高脂質血症は，血清コレステロール（Ch）とトリグリセリド（TG）の両方が増加し，リポ蛋白電気泳動でbroad βパターンを呈する比較的まれな高脂血症である．他の高脂血症がリポ蛋白の量的異常によるのに対し，本症ではその質的異常を伴う．さらに，動脈硬化症の合併率が高い反面，治療によく反応する高脂血症として以前から注目されてきた．本症で増加するリポ蛋白は，カイロミクロンやVLDLといったTG-richリポ蛋白に由来する異常なレムナント（β-VLDL）であり，その本質的な成因はアポEの異常である[1,2]．

■血清脂質・リポ蛋白の異常

III型高脂血症は血清コレステロールとトリグリセリドの両者が増加する．血清リポ蛋白での異常はβ-VLDLの出現・増加であり，それによるリポ蛋白電気泳動のbroad βパターンが本症を特徴づけている．

β-VLDLは，カイロミクロンやVLDLといったTG-richリポ蛋白に由来するレムナントで，VLDLの比重領域（$d<1.006$）にありながら電気泳動法でβ位置へ泳動される異常リポ蛋白である．III型高脂血症ではLDLの減少がみられる反面，このβ-VLDLや中間比重リポ蛋白（intermediate density lipoprotein：IDL）が血中に著しくうっ滞する．これらのレムナントは，コレステロールの含量も多く，血清コレステロールとトリグリセリド値が上昇する．III型高脂血症では，レムナントの増加に加えLDLの減少により血清リポ蛋白電気泳動像でbroad βパターンがより強調されることになる．

以上のように，III型高脂血症は，通常の場合，血中にほとんど認められないIDLや異常なレムナントであるβ-VLDLが増加し（質的異常），そのためリポ蛋白電気泳動でbroad βパターンを呈する特異な高脂血症と定義される．

■臨床症状

III型高脂血症は黄色腫と動脈硬化を高頻度に合

サイドメモ　β-VLDLとbroad βパターン

通常，VLDL（$d<1.006$）は電気泳動法でpre β位置に泳動される．これに対しVLDLの比重領域にありながらLDLの泳動部位であるβ位置へと泳動される異常リポ蛋白成分がβ-VLDLで，floating βともよばれる．TG-richリポ蛋白に由来する異常なレムナントで，動脈硬化促進作用が強い．正常のレムナントに比べ，著しくコレステロールエステルとアポEの含量が多い．

一般に，LDLは$1.006<d<1.063$の比重分画のリポ蛋白を意味するが，その大部分は$1.019<d<1.063$の比重分画に存在し（狭義のLDL），リポ蛋白電気泳動法でβ位置に泳動される．

一方，$1.006<d<1.019$の中間比重リポ蛋白（IDL）は，preβからβ位置へと泳動される．III型高脂血症ではIDLとβ-VLDLの増加があり，また，狭義のLDLは逆に減少している．このため，リポ蛋白電気泳動法ではこれらのリポ蛋白が重なり合い，preβからβ部位にかけて幅広いバンドが現れ，III型高脂血症に特徴的なbroad βパターンを呈する．

Familial type III hyperlipoproteinemia
Taku YAMAMURA：国立循環器病センター研究所病因部